REMARKS

Claims 1-3, 5-9, 11-14, and 17-52 are pending. Due to a restriction requirement, claims 2, 3, 5, 7-9, 11-14, 24-40, and 42-48 are withdrawn from consideration. In the action dated November 25, 2009, claims 1, 6, 17-23, 41, and 49-52 stand rejected under 35 U.S.C. § 103(a) as being obvious over Shimizu et al., J Biol Chem 276:49003-12, 2001 ("Shimizu") in view of U.S. Patent No. 5,814,603 ("Oldenburg") and PCT Publication WO 00/23594 ("Gardella"). These claims are also rejected on the basis of obviousness-type double patenting over claims 1, 7, and 23-29 of U.S. Patent Application No. 10/484,080 ("the '080 application) in view of Oldenburg. Each of these rejections is addressed below.

Restriction requirement

In the Restriction Requirement dated July 21, 2008, the Office required a species election of a peptide selected from the peptides of SEQ ID NOS:13-24, a fragment thereof, or an N- or C- derivative thereof. In response, Applicants elected SEQ ID NO:13. In the February 6, 2009 action, the Office conducted a search of SEQ ID NO:23 and found it to be free from the prior art, and the search was extended to SEQ ID NO:6. In the present action, claims 3 and 39, which recite the elected species, and claims 13 and 47, which recite SEQ ID NO:23, are withdrawn from consideration.

Because Applicants elected SEQ ID NO:13, examination of claims 3 and 39 is respectfully requested. Consideration of claims 13 and 47, which recite the peptide previously examined, is also requested on the grounds that doing so would not constitute an unreasonable burden.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 6, 17-23, 41, and 49-52 are rejected as being obvious over Shimizu in view of Oldenburg and Gardella. Claim 6 recites [desamino

Aib^1,Aib^3,Har^{11},Ala^{12},Trp^{14}]PTH(1-14)NH_2 and depends from claim 49. Shimizu is cited as teaching a PTH(1-14) peptide having α-aminoisobutyric acid (Aib) substitutions at positions 1 and 3 along with Har^{11}, Ala^{12}, and Trp^{14} substitutions. Oldenburg is cited as teaching that desamino PTH peptides resist protease degradation and have restricted conformation. Gardella is cited as teaching ^{99m}Tc- and ^{125}I-labeled PTH peptides. Based on these teachings, the Office concludes that the peptide of claim 6 would be obvious. This rejection is respectfully traversed.

As discussed in more detail below, the peptides of claim 1, which have a Trp, Bpa, or Arg at position 2, are free from this rejection because none of the cited references provide a reason to make such a substitution.

As also discussed in more detail below, the inventors have further made the surprising discovery that PTH peptides with α-helix-stabilizing residues at positions 1 and 3, when modified to remove the N-terminal amino group (i.e., the "desamino" peptides) or to have a Trp, Bpa, or Arg substitution at position 2, have *antagonist* and *inverse agonist* activity. Based on this surprising discovery, the peptides of claims 1, 49, and their dependent claims (including claim 6) are not obvious over the cited references.

The cited references teach only peptide agonists

Shimizu describes a PTH(1-14) peptide with Aib substitutions at positions 1 and 3 as having enhanced agonist activity. Oldenberg describes the effect of a Lys, Arg, Glu, or Gly substitution at each position of PTH(1-34) on cAMP-stimulating (i.e., agonist) activity and determines that certain positions of PTH, such as positions 1-10, lack tolerance for substitution (column 9, line 50, through column 10, line 25, and Figure 4). Gardella describes an alanine scan of the PTH(1-14) sequence and analysis of the substituted peptides for cAMP-stimulating activity (see Figure 5). Gardella also describes PTH(1-14)/PTHrP(1-14) peptides having substitutions at positions 1, 5, 8, 10, 11, or 14 (see page 7, lines 15-30). These references focus entirely on PTH receptor agonists.

The peptides of claim 1 are not obvious over the cited references

Even where claimed elements exist within the prior art, a reason to combine elements in a specific way is required in order to render a claimed invention obvious:

> a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.* (Emphasis added).

KSR v. Teleflex, 82 USPQ2d 1385, 1389 (2007). As set forth below, the cited references do not provide a reason to generate a peptide of claim 1 and thus cannot render this claim or its dependent claims obvious.

Claim 1 requires a peptide having (a) α-helix-stabilizing residues at positions 1 and 3 and (b) a Trp, Bpa, or Arg substitution at position 2. While Shimizu teaches that PTH(1-14) peptides having Aib at positions 1 and 3 exhibit enhanced activity, none of Shimizu, Oldenberg, or Gardella provides a reason to make a Trp, Bpa, or Arg substitution at position 2. Shimizu teaches that an Aib substitution at position 2 in PTH(1-14) results in a 470-fold reduction in cAMP activity (Table 1 on page 49006). Oldenberg teaches that positions 1-10 of the PTH(1-34) sequence are intolerant to substitution and that substitution of Arg, Glu, or Gly at position 2 substantially reduces PTH agonist activity (Figure 4). Gardella teaches that an alanine substitution at position 2 substantially reduces PTH(1-14) activity (Figure 5). These references, if anything, provide a strong suggestion against making a substitution at position 2. Because no combination of Shimizu, Oldenberg, and Gardella provides a reason to make a position 2 substitution, much less the claimed Trp, Bpa, and Arg substitutions, the claimed peptides cannot be obvious over these references. Withdrawal of this rejection, as applied to claim 1 and its dependent claims, is accordingly requested.

The peptides of claims 1, 49, and their dependent claims (including claim 6) have unexpected antagonist activity

The finding of an unexpected effect can render a claimed combination nonobvious. *KSR*, in its comments on *United States v. Adams* (383 U.S. 39 (1966)), supports a finding of nonobviousness in view of an unexpected result:

> The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was *not obvious* to those skilled in the art. (Emphasis added).

KSR at 1395.

Claim 6 is directed to a desamino PTH(1-14) analog having Aib substitutions at positions 1 and 3. As explained above, Shimizu is provided as teaching $Aib^{1,3}$-substituted PTH(1-14) peptides, and Oldenburg is provided as teaching that desamino peptides can resist protease degradation. On the basis of these teachings, the Office concludes it obvious to combine the substitutions of Shimizu with the desamino peptides of Oldenburg to arrive at the presently claimed peptides. Applicants respectfully disagree, as the claimed peptides exhibit unexpected antagonist and inverse agonist activity.

Importantly, neither Shimizu nor Oldenburg teaches or suggests the unexpected activity of peptides having a desamino modification at position 1 or a Trp, Bpa, or Arg substitution at position 2. These peptides act as antagonists against a PTH(1-14) agonist in HKRK-B28 cells (Figure 5). Similar results were observed in COS-7 cells transfected with the wild-type PTH-1 receptor and treated with the PTH(1-14) agonist (Figure 6A). When COS-7 cells were transfected with a modified PTH-1 receptor tethered to a PTH(1-9) peptide, inhibition by the desamino and the Trp^2, Bpa^2, or Arg^2 substituted peptides was also observed (Figure 6B). The claimed peptides thus have unexpected activity as PTH -1 receptor antagonists.

The claimed peptides also possess the unexpected property of activity as inverse agonists, i.e., they can reduce receptor activity in the absence of an agonist, as demonstrated using constitutively active PTH receptors. The desamino and the Trp^2, Bpa^2, or Arg^2 substituted peptides exhibited inverse agonist activity against the constitutively active H223R and H223R/T410P PTH-1 receptors (Figures 7A and 7C).

In addition to surprising antagonist and inverse agonist activity, the claimed peptides also exert these effects through a mechanism different from that of N-terminally truncated PTH antagonists described in the art, such as PTHrP(5-36) (Paragraph 8, page 3-4). The prior art antagonists bind to the extracellular N-domain of the PTH receptor. Because they lack the N-terminal amino acids that bind the J-domain, these peptides do not activate the receptor, as shown graphically in Figure 11A.

The present antagonists, by contrast, are C-terminally truncated peptides, and thus bind the J-domain, but do not activate the receptor. Evidence of this different mechanism of action is provided in Figure 8 and represented graphically in Figure 11B. The antagonist activity of a Bpa^2-containing antagonist was compared to the PTHrP(5-36) antagonist in cells expressing either the wild-type PTH-1 receptor or the delNt receptor, which lacks the extracellular N-domain. Both a PTH(1-34) analog and a PTH(1-14) analog were used as agonists. The PTH(1-34) agonist binds both the N- and J-domains, whereas the PTH(1-14) agonist binds only the J-domain. The PTHrP(5-36) peptide was more effective against the PTH(1-34) analog with the wild-type PTH receptor, due to its N-domain binding. PTHrP(5-36) does not effectively block J-domain binding, as evidenced by its weak antagonist activity against both the delNt receptor and the J-domain selective PTH(1-14) analog. By contrast, the Bpa^2-containing antagonist was effective against either analog with the delNt receptor and against the wild-type receptor treated with a PTH(1-14) analog. These results demonstrate the claimed peptides to be J-domain selective.

Thus, the claimed peptides exhibit antagonist and inverse agonist activity at the PTH-1 receptor and use a mechanism different from prior art antagonists in order to achieve this effect. Because none of the references cited by the Office teach or suggest these features, the activity of the claimed peptides is unexpected. On this basis, the present claims are nonobvious, and withdrawal of this rejection is respectfully requested.

Obviousness-type double patenting

Claims 1, 6, 17-23, 41, and 49-52 are rejected on the grounds of obviousness-type double patenting over claims 1, 7, and 23-29 of the '080 application in view of Oldenburg. This rejection is respectfully traversed.

The '080 claims recite PTH peptides having Aib substitutions at positions 1 and 3. Oldenburg is again cited as teaching that desamino peptides exhibit enhanced protease resistance. Based on these references, the Office concludes that claim 6 is obvious. Applicants respectfully traverse this rejection, for the reasons outlined above.

Claim 6, which depends from independent claim 49, recites the peptide, [desaminoAib^{1},Aib^{3},Har^{11},Ala^{12},Trp^{14}]PTH(1-14)NH_2. As explained above, the presently claimed peptides possess unexpected antagonist and inverse agonist activity, and mediate their effects through a mechanism different from the prior art antagonists. As these properties are unexpected over the '080 claims and over Oldenberg, these teachings cannot render the present claims obvious. Withdrawal of this rejection, as applied to claim 49 and its dependent claims, is respectfully requested.

Claim 1 recites a PTH peptide having a Trp, Bpa, or Arg substitution at position 2. Because neither the '080 claims nor Oldenberg suggest any reason to generate peptides having a substitution at position 2, claim 1 and its dependent claims cannot be obvious over this combination of teachings. Withdrawal of this rejection, as applied to claim 1 and its dependent claims, is also respectfully requested.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for one (1) month, to and including March 25, 2010, and authorization to charge the required extension fee to Deposit Account No. 03-2095.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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